to be a mistake – particularly in view of the rejections of record which are directed to claims 1-20. Clarification is respectfully requested.

1. Rejection of claims 1-4 and 7-20 under 35 U.S.C. §103(a) over Nishibe et al. (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628)

The Examiner has rejected claims 1-4 and 7-20 under 35 U.S.C. §103(a) over Nishibe et al. (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628).

In her rejection, the Examiner has stated, in relevant part:

> Nishibe et al. teach a ciclesonide containing sterile aqueous suspension sterilized by autoclaving (see abstract; addresses claim 1, 3 and 4). The suspension may comprise suspending agents and wetting agents such as hydroxypropylmethylcellulose (i.e. non-ionic excipients and suspending agents; see paragraphs 38 and 42; addreses claims 1, 9, 10, 11 and 13). Ciclesonide is dispersed in an aqueous medium including the excipients (see page 3, paragraph 42, lines 5-8) to give a white uniform aqueous suspension before being autoclaved at 115 degrees C for 30 minutes, at 121 degrees C for 20 minutes or at 126 degrees C for 15 minutes (see page 3, paragraph 43 and 49; addresses claims 15-19).
>
> Nishibe et al. does not specifically teach that the composition is suitable for nubulization (claim 1) nor that the composition comprises the specific non-ionic agent in claims 2, 7 and 8. Nishibe et al. also does not teach the osmolality range in claim 20...Nishibe et al. does not specifically teach the motivation for the specific suspending agent polysorbate (claim 14) nor the pH modifying agents of claim 12.
>
> Saidi et al. teach an aqueous composition to treat ailments and diseased (sic) of the respiratory tract, particularly the lungs, comprising a corticosteroid that can be delivered through a nebulizer (see abstract). The composition comprises an osmolality agent such as glucose such that the osmolality of the composition is from about 280-300 mosmol/kg (see column 7, lines 3-9; addresses claims 1, 7, 8 and 20). The composition also comprises a surfactant such as sorbitan esters (Tween series, i.e. polysorbate; see column 8, line 57, addresses claim 14).

Lintz et al. teach pharmaceutical kits for the preparation of liquid composition (sic) that are administered as aerosols through nebulization (see abstract and paragraph 18). Drugs to be delivered include ciclesonide (see paragraph 19) that can be administered with excipients such as citric acid and tartaric acid to adjust the pH (see paragraph 25) and surfactants to increase the wettability of the active compound or to improve the dissemination of the aerosol droplets in the lungs (see paragraph 27). Preferable surfactants include Tween 60 (i.e. polysorbate; see paragraph 27, last two lines).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Nishibe et al. and providing the composition in a nebulizer because Saidi et al. teach that compositions can be made with corticosteroids to be delivered through a nebulizer to provide treatment for ailments and diseases of the respiratory tract (see abstract).

To one of ordinary skill in the art at the time of the invention would have found (sic) it obvious and motivated to combine the method of Nishibe et al. and providing the osmolality agents of claims 2, 7 and 8 and at the osmolality range of claim 20 because Saidi et al. teach nebulizer compositions comprising corticosteroids that have an osmolality agent such as glucose such that the osmolality of the composition is from about 280-300 mosmol/kg (see column 7, lines 3-9). Buffers may be used to adjust the pH (see column 6, lines 64-66).

To one of ordinary skill in the art at the time of the invention would have found (sic) it obvious and motivated to combine the method of Nishibe et al. in view of Saidi et al. and providing an organic acid of claim 12 as a pH modifying agent because Saidi et al. and Lintz et al. teach that a nebulized composition of drugs such as ciclesonide can be administered with pH modifiers. Particularly, Lintz et al. teach that organic acids such as citric and tartaric acid ... adjust the pH (see abstract and paragraphs 18, 19 and 25).

RESPONSE

Applicant respectfully traverses this rejection of claims 1-4 and 7-20. The Examiner has not established a *prima facie* case of obviousness against these claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *See KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicant respectfully submits that a *prima facie* case of obviousness has

not been established against the presently pending claims because 1) a person of ordinary skill in the art would not combine the teachings of Nishibe et al., Saidi et al. and Lintz et al.; and 2) even if a person of ordinary skill in the art would combine the teachings of these references, she would find no motivation in the cited references to choose only "non-ionic excipients" as presently claimed.

A. There is no motivation to combine the Nishibe et al., Saidi et al. and Lintz et al. references.

Applicant respectfully submits that a person of ordinary skill in the art would not be motivated to combine the teachings of the Nishibe et al., Saidi et al. and Lintz et al. references to arrive at the presently pending claims.

The presently pending claims are directed to a method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of:

a. providing an aqueous suspension of ciclesonide, containing one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and

b. autoclaving the aqueous suspension provided in (a).

As stated by the Examiner on page 3 of the Official Action, the suspension that is taught by Nishibe et al. is not suitable for nebulization because it does not contain an agent for adjusting the osmolality of the suspension. However, Nishibe et al. does refer to some of the problems associated with autoclaving. In

particular, Nishibe et al. address the issue of "drug content uniformity" in paragraph [0014] and explain that the uniformity

> "of [an] aqueous suspension containing a water-insoluble drug tends to be depressed by autoclaving, even if the drug is chemically stable. Such a phenomenon, the depression of content uniformity, is explained that some particles of water-insoluble drug that are once dissolved or partly dissolved to smaller particles under such high temperature appeared again as various size of particles during subsequent cooling, leading to wider range of particle size distribution in suspension."

Therefore, starting with the Nishibe et al. reference, the person of ordinary skill in the art is faced with the technical problem of providing a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration.

The presently claimed method requires that the "sterile aqueous suspension of ciclesonide" is "suitable for nebulization" after autoclaving. The Examiner attempts to remedy the deficient teachings of the Nishibe et al. reference by using the Saidi et al. reference which does discuss nebulization but does not have any teaching regarding autoclaving.

Instead, the compositions disclosed in Saidi et al. are all sterilized by use of a 0.22 micron sterile filter and not by autoclaving. Clearly, a reference that does not even teach autoclaving cannot provide any motivation to solve the technical problems associated with autoclaving – namely to provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. Therefore, a person of ordinary skill in the art would not look to the Saidi et al.

reference to remedy the deficient teachings of Nishibe et al. to arrive at the presently pending claims.

Similarly, the compositions disclosed in Lintz et al. are sterilized by use of a 0.22 micron sterile filter and not by autoclaving. Again, a reference that does not even teach autoclaving cannot provide any motivation to solve the technical problems associated with autoclaving – namely to provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. Therefore, a person of ordinary skill in the art would not look to the Lintz et al. reference to remedy the deficient teachings of Nishibe et al. and/or Saidi et al. to arrive at the presently pending claims.

Accordingly, it is improper hindsight reconstruction for the Examiner to combine the teachings of the Nishibe et al., Saidi et al. and Lintz et al. references to allege that the presently pending claims are obvious.

B. There is no teaching in the Nishibe et al., Saidi et al. and Lintz et al. references to select only non-ionic agents

Assuming arguendo that a person of ordinary skill would look to the combined teachings of Nishibe et al., Saidi et al. and Lintz et al., they would find no motivation to select only the presently claimed "non-ionic" agents to arrive at the presently pending claims.

The Examiner alleges on page 4 of the Official Action, in relevant part, that

> To one of ordinary skill in the art at the time of the invention would have found (sic) it obvious and motivated to combine the method of Nishibe et al. and providing the osmolality agents of claims 2, 7 and 8 and at the osmolality range of claim 20 because Saidi et al. teach nebulizer compositions comprising corticosteroids that have an osmolality agent such as glucose such that the osmolality of the composition is from about 280-300 mosmol/kg (see column 7, lines 3-9). Buffers may be used to adjust the pH (see column 6, lines 64-66).

However, the section of the Saidi et al. reference that the Examiner refers to at column 7, lines 3-9 actually teaches the addition of an osmotic agent generally with no recognition that the presently claimed non-ionic agents provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. Specifically, Saidi et al. teach that "such agents include **any** low molecular weight water-soluble species pharmaceutically approved for pulmonary and nasal delivery such as **sodium chloride** and glucose." (emphasis added).

However, it is clear that ionic osmotic agents such as sodium chloride do not successfully render the presently claimed "sterile aqueous suspension of ciclesonide suitable for nebulization". In this regard, applicant respectfully directs the Examiner's attention to Example 7 on page 11 of the instant specification. In Example 7, a comparison was made between two formulations:

Formulation I contained 0.05% micronized ciclesonide, 0.025% Polysorbate 20 as suspending agent and 0.9% sodium chloride.

Formulation VII contained only 0.05% micronized ciclesonide and 0.025% Polysorbate 20 as suspending agent.

After sterilization of each Formulation, it was shown that the suspension that contained no ionic agent (i.e. sodium chloride) exhibited no significant increase in the particle size. Conversely, the suspension containing the ionic agent rendered "Large white agglomerates". Such agglomerates are not suitable for nebulization.

In view of the clear lack of teaching or suggestion contained in the cited references regarding the selection of only non-ionic agents in the presently claimed method, the presently pending claims are not obvious over the cited references.

Reconsideration and withdrawal of this rejection is respectfully requested.

2. Rejection of claim 5 under 35 U.S.C. §103(a) over Nishibe et al. (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and in further view of Wurst et al. (US 2007/00259230)

The Examiner has rejected claim 5 under 35 U.S.C. §103(a) over Nishibe et al. (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) as applied to claims 1-4 and 7-20 and further in view of Wurst et al. (US 2007/00259230).

In her rejection, the Examiner has stated, in relevant part:

> Nischibe (sic) et al., Saidi et al. and Lintz et al. do not teach the ciclesonide derivatives of claim 5.
>
> Wurst et al. teach that the 21-hydroxy derivative of ciclesonide...is the active metabolite of ciclesonide (see page 1, paragraph 6).
>
> To one of ordinary skill in the art at the time of the invention would

have found (sic) it obvious and motivated to combine the method of Nishibe et al. in view of Saidi et al. and providing the ciclesonide derivatives of claim 5 because of Wurst et al. teach that the 21-hydroxy derivative of ciclesonide...is the active metabolite of ciclesonide (see page 1, paragraph 6).

RESPONSE

Applicant respectfully traverses this rejection of claim 5. The Examiner has not established a *prima facie* case of obviousness against these claims.

First, for the sake of brevity, applicant incorporates by reference all arguments presented in section 1 of this Response. As shown in section 1 of this Response, a *prima facie* case of obviousness has not been established against the presently pending claims because 1) a person of ordinary skill in the art would not combine the teachings of Nishibe et al., Saidi et al. and Lintz et al.; and 2) even if a person of ordinary skill in the art would combine the teachings of these references, she would find no motivation in the cited references to choose only "non-ionic excipients" as presently claimed.

The Examiner is correct that the Nishibe et al., Saidi et al. and Lintz et al. references do not teach the ciclesonide derivatives recited in claim 5. However, the Examiner may not use the Wurst et al. reference to remedy the deficient teachings of these cited references. Wurst et al. is only available as prior art against the present application under 35 U.S.C. §102(e). In particular, Wurst et al. has an earliest priority date of September 16, 2003 and was published February 1, 2007, whereas the present application has an earliest priority date of December 16, 2003.

The Wurst et al. application and the present application were, at the time the claimed subject matter was made, commonly owned, and thus falls within the 35 U.S.C. §103(c) exception. Accordingly, the Wurst et al. reference cannot be used as prior art against the present application.

Reconsideration and withdrawal of this rejection is respectfully requested.

3. Rejection of claim 6 under 35 U.S.C. §103(a) over Nishibe et al. (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and in further view of Sambuco et al. (US 2005/0175546)

The Examiner has rejected claim 6 under 35 U.S.C. §103(a) over Nishibe et al. (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) as applied to claims 1-4 and 7-20 and further in view of Sambuco et al. (US 2005/0175546).

In her rejection, the Examiner has stated, in relevant part:

> Nischibe (sic) et al., Saidi et al. and Lintz et al. do not teach the particle size of ciclesonide as in claim 6.
>
> Sambuco et al. teach an aqueous suspension of sterile micronized drug particles particularly corticosteroids such as ciclesonide, administered by inhalation, which produces homogenous dispersions of particles characterized by optimal size and size distribution (see abstract and paragraph 29). The particles are preferably less than 7µm (see paragraph 33), which can more easily dissolve in the lung fluids and penetrate into the cells in a better way, giving rise to a prolonged activity (see paragraph 39).

RESPONSE

Applicant respectfully traverses this rejection of claim 6. The Examiner

has not established a *prima facie* case of obviousness against these claims.

First, for the sake of brevity, applicant incorporates by reference all arguments presented in section 1 of this Response. As shown in section 1 of this Response, a *prima facie* case of obviousness has not been established against the presently pending claims because 1) a person of ordinary skill in the art would not combine the teachings of Nishibe et al., Saidi et al. and Lintz et al.; and 2) even if a person of ordinary skill in the art would combine the teachings of these references, she would find no motivation in the cited references to choose only "non-ionic excipients" as presently claimed.

The Examiner is correct that the Nishibe et al., Saidi et al. and Lintz et al. references do not teach the particle size of ciclesonide recited in claim 6. However, as stated above in section 1, the Nishibe et al., Saidi et al. and Lintz et al. references do not render claims 1-4 and 7-20 obvious. Therefore, the Sambuco et al. reference would have to have some teaching that would cure the deficiencies of the other cited references, which it does not.

In particular, Sambuco et al. does not address any of the technical problems associated with autoclaving - namely to provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization. The only disclosure contained in Sambuco et al. regarding autoclaving is a cursory identification of autoclaving as one of many processes that can be used to manufacture sterile formulations for inhalation. See paragraph [0010] of Sambuco, et al.:

> [0010] Various processes can be used to manufacture sterile pharmaceutical formulations for inhalation. For example, the active ingredient can be sterilised by dry heating or irradiation, followed by preparation of the formulation under aseptic conditions, or the formulation can be pre-prepared and sterilised by treatment in an autoclave or by filtration.

Further, Sambuco et al. has no teaching that would motivate the skilled artisan to select only the presently claimed "non-ionic" agents to arrive at the presently pending claims.

Sambuco et al. therefore, has no teaching that would cure the deficiencies of the Nishibe et al., Saidi et al. and Lintz et al. references.

Reconsideration and withdrawal of this rejection is respectfully requested.

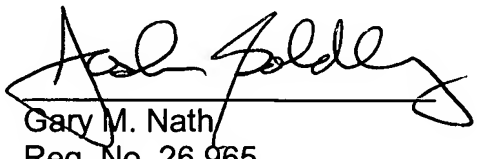
CONCLUSION

In view of the foregoing, applicant respectfully requests that the Examiner reconsider and withdraw the rejections of record and to allow pending claims 1-20 to proceed to grant.

If the Examiner has any questions or wishes to discuss this matter, the Examiner is welcomed to telephone the undersigned attorney.

In the event this paper is not timely filed, applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,
THE NATH LAW GROUP



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